

REMARKS

This Preliminary Amendment and Remarks are filed concurrently with filing the Request for Continuing Examination and is in response to the Advisory Action issued on December 12, 2003 wherein Examiner rejected claims 19, 21-25, 40, 41 and 43-49 and objected to claims 20 and 42.

Status of the Amended Claims

Claims 19, 21-25, 40, 41 and 43-49 are as previously presented. Claims 50 and 51 are two newly added independent claims corresponding to prior claims 20 and 42 objected to by the Examiner but found allowable if redrafted in the independent form.

Rejections Under 35 USC 102(a)

Examiner previously rejected Claims 19-24 and 40-49 in the Final Office Action under 35 USC 102(a) as being anticipated by Nesterenko et al.

Examiner maintained his prior rejections and argued that Nesterenko discloses antibodies that bind to a surface antigen proteinase of 24kD associated with sporozoites of *Cryptosporidium parvum* from fecal specimens, that this surface antigen protease was inhibited by inhibitors of both metalloproteinases and thiol proteinases, but not serine or aspartyl proteinase inhibitors, that the sensitivity of the membrane-associated cysteine protease to inhibitors is similar to that of the metallo-activated cysteine proteinases calpain I and II and, therefore, the evidence seems to

suggest that Nesterenko's cysteine protease is the same antigen that comprises SEQ ID NOS: 4-6 of the instant application, and antibodies to this antigen inherently meet the limitations of the instant claims given the evidence at hand and absent evidence to the contrary.

Applicants disagree and will deal with Examiner rejections and response to prior Applicants arguments in the same sequence as raised by the Examiner.

First, Applicants amended claims 19, 21-25, 40, 41 and 43-49 to be directed to the antibody against cryptopain antigen depicted solely by the amino acid sequences SEQ ID NOS: 4-6 and additionally added two new independent claims which Examiner indicated would be allowable if redrafted in the independent form. The claimed antigen is specifically identified as 401 amino acid protein of 45 kD, depicted by SEQ ID NO: 4 or as its fragment SEQ ID NOS: 5 or 6, which are specifically identified as having a MW 25 kD. Applicants respectfully submit that the claimed antibody is not the same antibody as that of antibody disclosed by Nesterenko.

The Nesterenko protease is described as 24 kD, compared to the cryptopain protease having a molecular weight of 45 kD. Nesterenko does not identify it as a fragment but as a whole protease having that size. Applicants, on the other hand identify the whole cryptopain protease as having 45 kD (page 10, lines 28-33, page 11, lines 1-5) with its mature portion of 226 amino acid protein of MW

25 kD. The DNA sequence of 1203 nucleotides encodes the 45 kDa protein SEQ ID NO: 4, the cathepsin-like cysteine proteinase cryptopain (page 12, lines 24-27).

Examiner dismisses the difference in the MW between the Nesterenko protease and currently claimed cryptopain as irrelevant and due to a laboratory experimental error, but it is not so. One cannot mix apples and oranges at will. If the compared subject is the whole protein, and the cryptopain protease is the whole protein, then the respective molecular weights and the behavior and/or presence of such protein and their metallo-dependency or independency are also important in distinguishing the invention from the reference. In this case, the applicants whole protein has MW 45 kD and its fragments' MW is 25 kD. The current cryptopain is metallo-independent either surface or internally localized antigen. Nesterenko's protease has MW 24 kD, is a surface antigen and metallo-dependent.

As to the molecular weight, one dalton is defined as a unit mass equal to 1.65×10^{-24} gm. One kilodalton is 1000 times that amount. The difference in molecular weight between $24 \times 1.65 \times 10^{-24} \times 1000$ of Nesterenko protease (39,600 mass units) and 45 or $25 \times 10^{-24} \times 1000$ of the cryptopain (74,250 or 41,250 mass units) is either 34,650 mass units for 45 kD protein or 2,350 mass units for 25 kD protein.

If the compared subject is the antibody raised against the

specific antigen, such as the one disclosed by Applicants having a very precise and specific amino acid sequence and molecular weight of 45 kD, 34,650 mass units larger, or 25 kD, 2,350 mass units larger than the protein of the Nesterenko reference, then the difference in the molecular weight cannot be valiantly dismissed as unimportant due to the laboratory error. Examiner does not present any evidence showing that the 45, 25 and 24 kD proteins are the same and/or that there was an experimental error in Applicants' determination of amino acid or DNA sequences of relevant proteins SEQ ID NOS: 4-6.

Applicants maintain that 24 and 25 and 45 kD proteins are not the same and that cryptopain of the invention is not protease of Nesterenko and therefore the antibody raised against cryptopain are not the same as those raised against protease of Nesterenko.

Applicants now amended claims only to the antibodies raised against the antigen having those specific amino acid sequences and different molecular weight from the protease of Nesterenko.

Moreover, the claimed antibodies are raised against the recombinant molecules thus even further distinguishing them from the proteases of Nesterenko whose antibodies were eluted directly from nitrocellulose blots (Abstract) or produced naturally (page 80, last full paragraph and page 81, the first paragraph).

Examiner further responded to prior Applicant's arguments filed February 24, 2003 having not found them persuasive because

Applicant argues that Nesterenko's antibodies were not associated with oocyst walls, rhoptries or micronemes which are internal structures and the surface localization of Nesterenko's antibodies is consistent with the Examiner's observation that Nesterenko's antibodies bound to a surface antigen protease.

Although in view of the new amendments and arguments showing that the current cryptopain is different than the protease of Nesterenko, this argument is moot, Applicants want to point out that, unfortunately, Examiner's observations cannot be used to support otherwise unrefutable evidence stated by both the Nesterenko and by the Applicants. The fact remains that the Applicants cryptopain is found either on the surface or internally positioned and gets to the surface during the invasion as shown by the use and testing of specific inhibitors as shown in Figure 10, as discussed in greater detail in the prior response to the Office Action. Applicants do not say that their protease is the surface or is not the surface, only that their results show that it can be surface or it can be internal antigen which may be released during the invasion. That is not the same as Nesterenko who clearly states in the Abstract: "An indirect immunofluorescence assay using these monospecific antibodies revealed that the protease occurred on the surface of sporozoites, but was not associated with oocyst walls, rhoptries or micronemes." (Abstract)

Examiner finds the simpler explanation for the experimental

results seen in Figure 10 that, to make the reasonable conclusion based on the evidence that cryptopain is a surface antigen, absent evidence to the contrary, such data explicitly show its internal location or translocation to the surface.

Applicants again disagree. Based on above showing that the cryptopain is different protease from that of Nesterenko, the above conclusion is moot as Applicants do not claim either the surface or internally located antigen but a specific antibody raised against antigens with known amino acid sequence and molecular weight.

Finally, Examiner rejects Applicant's prior argument that cryptopain is a cathepsin-like cysteine proteinase and is distinguished from the proteinase of Nesterenko which is inhibited by inhibitors of metalloproteinases and thiol proteinases.

Applicants again disagree. The fact that the cryptopain is not metalloproteinase dependent is just another distinguishing feature in showing that the protease of Nesterenko and the current cryptopain. Applicants do not claim this property and, other then showing that the two proteases have different properties vis-a-vis metalloproteinase inhibitors, it has no bearing on the current claims.

Applicants respectfully submit that the protease of Nesterenko is not the same and is not anticipated by Nesterenko. All evidence points to the contrary. Section 102 (a) requires that the invention is known or used or patented or described, in other words, that the

two are the same. This is clearly not the case here.

Examiner is respectfully requested to withdraw the rejection under 35 USC 102 (a) and pass the claims to issue.

Rejections Under 35 USC 103(a)

Claims 19-22 and 25 are rejected under 35 USC 103(a) as being unpatentable over Nesterenko in view of Ramakrishnan et al. (US 5,817,310).

Examiner argues that the teachings of Nesterenko are set forth above. Nesterenko does not teach monoclonal antibodies. Ramakrishnan does teach the advantage of monoclonal antibodies which can be produced from immortalized cell lines which would then allow unlimited production of antibodies. It would have been obvious to one of ordinary skill in the art at the time of the invention to make monoclonal antibodies to any pathogen in order that the supply of said antibodies would be steady and constant from an immortalized cell line.

Applicant's arguments filed February 24, 2003 have been fully considered but they are not persuasive because Applicant argues the antibodies of Nesterenko do not meet the claim limitations for the reasons argued in the 102(a) rejection set forth above. The Examiner believes he has successfully responded to these arguments above and so the rejection is maintained.

Applicants disagree.

Applicants have shown that the protease of Nesterenko is not

the same as cryptopain of the invention. Cryptopain has not the same molecular weight, may be localized differently and is not metalloproteinase dependent. Therefore, any combination of the Nesterenko reference with the teaching of Ramakrishnan would derive, at most, a monoclonal antibodies to the Nesterenko 24 kD protease but it will not result in the monoclonal antibodies of the invention raised against the whole cryptopain or the fragment thereof.

Applicants respectfully request that in view of the above presented arguments Examiner reconsiders his rejection under 35 U.S.C. 102 and 103 and allows the pending claims to issue.

SUMMARY

In summary, Applicants resubmit previously amended claims 19, 21-25, 40, 41 and 43-49 and added two independent claims which Examiner indicated would be allowable and submit compelling arguments overcoming the rejections under 35 U.S.C. 102 and 103. With these rejection being overcome, Applicants believe that all claims are in conditions for immediate allowance. Notice of Allowance is respectfully solicited.

Should Examiner require further amendments, Examiner is requested to call the undersigned at 650-324-1677.

Respectfully submitted,

Date: January 19, 2004



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